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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,037	07/23/2003	Warren J. Scherer	512-160	1255

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,037	SCHERER, WARREN J.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *29Jun10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 11 and 36 are presented for examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's payment and submission filed May 4, 2010 was received and entered into the present application. Accordingly, prosecution has been reopened.

Applicant's Information Disclosure Statement (IDS) filed June 29, 2010 (two pages total) has been received and entered into the present application. As reflected by the attached, completed copies of form PTO/SB/08a, the Examiner has considered the cited references.

Claims 11 and 36 remain pending and under examination. Claim 36 is amended.

Applicant's arguments, filed May 4, 2010, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 36 is directed to a method of treating facial flushing associated with menopause-associated hot flashes in a human in need thereof, the method comprising topically administering a composition comprising an effective amount of a single active component that reduces cutaneous facial flushing, wherein the single active component consists of brimonidine tartrate and a dermatologically acceptable carrier, locally to facial skin of the human, wherein the brimonidine tartrate acts locally to reduce cutaneous facial flushing.

In particular, the claim(s) as presently written fail to set forth the identity of the "activity" of the "single component" such that it would have been clear as to what components are included and/or excluded from the instant claims. For example, it is unclear if the "activity" of the component is its ultimate physiological effect on facial flushing or if it is the mechanism by which the compound functions to treat the facial flushing (i.e., that the compound functions as an alpha-2 adrenergic receptor agonist). In addition, this ambiguity in the claims is further complicated by the fact that instant claim 11 further provides for the use of other agents that clearly possess an "activity" in the sense that they are, e.g., antibacterial agents, antioxidant agents, etc. The present of such additional components confuses the determination of what would be considered an "active component" of the claims and what would not be considered an "active" component of the claims. Additionally, the "dermatologically acceptable carrier" has its own activity as a carrier to provide the brimonidine tartrate compound and, thus, would also be considered an "active component" as well. As a result of these ambiguities of the claim, it is not clearly, precisely or deliberately set forth in the claims exactly what constitutes an "active component" such that it would be clear what components are intended to be included and what components are excluded from the claims as presently written. Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is required.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination, the claims will be interpreted to read on the "active component" to circumscribe components with alpha-2 adrenergic receptor agonist activity such that the limitation directed to "a single active component" that is brimonidine tartrate is intended to mean that there is only one "active component" administered to the human in need thereof that functions as an alpha-2 adrenergic agonist. Applicant is urged to clarify the identity of the "activity" of the "single active component" as recited in the claims for the reasons set forth *supra*.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al. (WO 02/36144; May 2002) in view of Gil et al. (U.S. Patent Application Publication No. 2003/0229088; Issued December 2003, Filed May 2002), Wymenga et al. ("Management of Hot Flushes in Breast Cancer Patients", *Acta Oncologia*, 41(3); 2002:269-275) and Ito (EP 10069124 A1; 200), each already of record.

Arnold et al. teaches a medicament comprising one or more GnRH analogue compounds, optionally in combination with an estrogen or progestin compound, which may also be formulated in combination with at least one compound selected from, *inter alia*, alpha-adrenergic agonists (p.12, l.20-31). Arnold et al. further teaches that said medicament is useful for the treatment of side effects of ovarectomy or symptoms associated with reproductive senescence in female mammals (i.e., menopause;

p.9, l.25-30), in particular, women (p.11, l.9-14), wherein such symptoms include vasomotor symptoms, especially hot flushes (p.10, l.10-14), and may be prepared in the form of creams or foams (p.15, l.6-12).

Though Applicant's amendment to instant claim 36 to now specify that the composition to be topically applied to the affected skin comprises an effective amount of a "single active component", wherein the single active component is brimonidine tartrate, is noted, Applicant has failed to clearly set forth the identity of the "activity" such that it would be clear to one of skill in the art what compounds would be excluded from the instant claims. Absent a precise description of what components would be included and/or excluded from the instant claims, a clearly reasonable interpretation of the claim is that the "activity" of the single active component is the actual mechanism by which the component functions, i.e., in the instant case, that the component is an alpha-2 adrenergic agonist, such that the claimed composition to be applied would contain a single (i.e., the only) alpha-2 adrenergic agonist to be administered. This is clearly met by the teachings of Arnold et al., who discloses the use of a GnRH analogue compound (i.e., not an alpha-2 adrenergic agonist) with an (i.e., one) alpha-2 adrenergic agonist and, therefore, the reference still applies as relevant prior art over the instant claims, absent factual evidence to the contrary and further absent any explanation as to what particular "activity" is intended to be circumscribed by the phrase "single active component".

Arnold et al. fails to teach (1) the use of brimonidine tartrate as the alpha-adrenergic agonist (claim 36); (2) topical administration of the composition locally to the facial skin (claim 36); or (3) the concomitant use of an additional agent as provided for in instant claim 11.

Gil et al. teaches known alpha-adrenergic agonists, including clonidine, brimonidine, tizanidine, etc. (p.1, para.[0009]) and salts thereof, including the tartrate salt (p.13, para.[0091]), and compositions thereof (p.13, para.[0096]) in dermatologically acceptable formulations, such as, e.g., a dermal patch, topical drops, creams, gels, or ointments, etc. (p.14, para.[0099]).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ the alpha-adrenergic agonist brimonidine or a salt thereof (such as, e.g., the tartrate salt of brimonidine) in the medicament disclosed by Arnold et al. as effective for the treatment of hot flashes that result from reproductive senescence in women because Gil et al. teaches that brimonidine (or its tartrate salt, for example) is one of a finite number of alpha-adrenergic agonists known in the prior art at the time of the invention to predictably function as agonists of alpha-adrenoreceptors. In other words, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ any one of the known alpha-adrenergic agonists (which, as evidenced by Gil et al., included brimonidine tartrate) into this formulation of Arnold et al. with a reasonable expectation of success because (1) a person with ordinary skill in the art has good reason to pursue known options within his or her technical grasp and (2) Arnold et al. teaches the desirability of including such an alpha-adrenergic agonist into the disclosed GnRH analogue formulation for the treatment of hot flashes that result from reproductive senescence in women.

Wymenga et al. teaches that menopausal flushing onset is abrupt and typically starts with a feeling of heat in the upper body that is generally associated with a visible reddening of the face (col.1, para.4, p.270). Wymenga et al. further teaches that administration of vitamin E (i.e., an antioxidant; see instant claim 11) in an amount of 800 I.U. per day to patients experiencing hot flushes demonstrated a significant reduction in flushing, which, though on average was only a reduction in one flushing incident per day, was still suggested for use in treating hot flushes due to its non-toxic and inexpensive properties, as well as the fact that it is widely available (col.2, para.2, p.272).

Ito teaches compounds and pharmaceutical composition containing said compounds in an effective amount and a pharmaceutically acceptable carrier (p.5, para.[0026]), and are useful for the treatment of disorders or medical conditions, such as inflammatory diseases (p.2, para.[0001]), wherein the condition to be treated is, *inter alia*, vasomotor disturbances including hot flushes (p.5, para.[0027]).

Ito teaches that the compounds may be administered via topical administration for treatment of the disclosed diseases (p.14, para.[0071]) and should be administered topically when treating inflammatory conditions of the skin, preferably by way of creams, gels, pastes, ointments, etc. (p.14, para.[0076]).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to apply the cream or foam formulation of Arnold et al. topically to the site of the facial flushing in a patient experiencing menopausal-related hot flashes because (1) menopause-associated hot flashes result in visible reddening of the face, as evidence by Wymenga et al., (2) treatment of diseases including hot flushes, as well as inflammatory conditions of the skin, should be treated topically, as evidenced by Ito, and (3) the skilled artisan would have recognized the advantage to directly treating the area of flushing with a topical formulation effective to treat such flushing by applying it directly to the affected area of skin, such as, e.g., directly to the face to treat facial flushing resulting from menopausal hot flashes, absent factual evidence to the contrary. Such a person would have been motivated to do so in order to treat the affected area while minimizing exposure of unaffected areas to the pharmacologic formulation.

Furthermore, one of skill in the art at the time of the invention would have also found it *prima facie* obvious to combine the formulation of Arnold et al. in view of Gil et al. with the vitamin E compound in light of the disclosure of Wymenga et al. because Wymenga et al. teaches the activity of vitamin E in effecting a significant reduction in the incidence of menopausal hot flushes and, thus, the cutaneous flushing associated therewith. Motivation to administer both compounds/compositions together flows logically from the very fact that each discrete agent was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two agents, when combined, would have, at minimum, additive, if not synergistic, effects in reducing the incidence of menopausal hot flushes (and the cutaneous flushing that results from the same) when combined. Please see *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980) ["It is *prima facie*

obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."] and *In re Diamond and Kellman*, 149 USPQ 562 (CCPA 1966).

Conclusion

Rejection of claims 11 and 36 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Primary Examiner, Art Unit 1614

September 23, 2010